

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently Amended) An antibody comprising a single-chain polypeptide ~~having binding activity against~~ that binds to the thrombopoietin (TPO) receptor (Mpl), wherein said antibody comprises two heavy chain variable regions and two light chain variable regions, and at least one of the heavy chain variable regions comprises a set of CDR1, CDR2 and CDR3 sequences selected from the group consisting of:

- (a) SEQ ID NOs: 3, 4, and 5;
- (b) SEQ ID NOs: 6, 7, and 8;
- (c) SEQ ID NOs: 9, 10, and 11;
- (d) SEQ ID NOs: 15, 16, and 17;
- (e) SEQ ID NOs: 18, 19, and 20;
- (f) SEQ ID NOs: 21, 22, and 23;
- (g) SEQ ID NOs: 24, 25, and 26;
- (h) SEQ ID NOs: 27, 28, and 29;
- (i) SEQ ID NOs: 30, 31, and 32;
- (j) SEQ ID NOs: 33, 34, and 35;
- (k) SEQ ID NOs: 36, 37, and 38;
- (l) SEQ ID NOs: 39, 40, and 41;
- (m) SEQ ID NOs: 42, 43, and 44;
- (n) SEQ ID NOs: 48, 49, and 50;
- (o) SEQ ID NOs: 51, 52, and 53;
- (p) SEQ ID NOs: 54, 55, and 56; and
- (q) SEQ ID NOs: 57, 58, and 59.

2. (Currently Amended) The antibody of claim 1, wherein the two heavy chain variable regions and the two light chain variable regions are arranged in the order, from the N-terminus of the single-chain polypeptide, of heavy chain variable region, light chain variable region, heavy chain variable region, and light chain variable region ~~from the N-terminus of the single-chain polypeptide~~.

3. (Currently Amended) The antibody of claim 1, wherein the ~~two heavy chain~~ four variable regions ~~and the two light chain variable regions~~ are linked by linkers.

4. (Currently Amended) The antibody of claim 3, wherein ~~the linkers~~ each linker comprises 15 amino acids.

5. (Canceled)

6. (Currently Amended) The antibody of claim [[5]]1, which is a humanized antibody.

7. (Canceled)

8. (Currently Amended) The antibody of claim 1, wherein the [[An]] antibody ~~that~~ binds to soluble Mpl.

9. (Withdrawn) An antibody that binds to human Mpl or monkey Mpl.

10. (Withdrawn) An antibody having agonistic activity against human Mpl or monkey Mpl.

11. (Currently Amended) The [[An]] antibody of claim 1, wherein the antibody binds whose binding activity to soluble Mpl [[is]] with a  $KD = 10^{-6}$  M or lower.

12. (Currently Amended) The [[An]] antibody of claim 1, wherein the antibody binds whose binding activity to soluble Mpl [[is]] with a  $KD = 10^{-7}$  M or lower.

13. (Currently Amended) The [[An]] antibody of claim 1, wherein the antibody has a whose TPO agonistic activity [[is]] of  $EC50 = 100$  nM or lower.

14. (Currently Amended) The [[An]] antibody of claim 1, wherein the antibody has a whose TPO agonistic activity [[is]] of  $EC50 = 30$  nM or lower.

15. (Currently Amended) The [[An]] antibody of claim 1, wherein the antibody has a whose TPO agonistic activity [[is]] of  $EC50 = 10$  nM or lower.

16. (Canceled)

17. (Currently Amended) The antibody of claim 32 that comprises a light chain variable region, wherein said light chain variable region comprises CDR1, CDR2 and CDR3 consisting of an amino acid sequence of any one of 1, wherein at least one of the light chain variable regions comprises a set of CDR1, CDR2 and CDR3 sequences selected from the group consisting of:

- (a) SEQ ID NOs: 60, 61, and 62;
- (b) SEQ ID NOs: 63, 64, and 65;
- (c) SEQ ID NOs: 78, 79, and 80;
- (d) SEQ ID NOs: 84, 85, and 86;
- (e) SEQ ID NOs: 93, 94, and 95;
- (f) SEQ ID NOs: 96, 97, and 98;
- (g) SEQ ID NOs: 102, 103, and 104;

- (h) SEQ ID NOs: 108, 109, and 110;
- (i) SEQ ID NOs: 111, 112, and 113; and
- (j) SEQ ID NOs: 114, 115, and 116.

18. (Currently Amended) The antibody of claim 32 ~~that comprises a heavy chain variable region and a light chain variable region of 1 comprising~~ any one of:

(a) ~~[[a]] heavy chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 3, 4, and 5, respectively,~~ and ~~[[a]] light chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 60, 61, and 62, respectively;~~

(b) ~~[[a]] heavy chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 6, 7, and 8, respectively,~~ and ~~[[a]] light chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65, respectively;~~

(c) ~~[[a]] heavy chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 9, 10, and 11, respectively,~~ and ~~[[a]] light chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65, respectively;~~

(d) ~~[[a]] heavy chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 15, 16, and 17, respectively,~~ and ~~[[a]] light chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65, respectively;~~

(e) ~~[[a]] heavy chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 18, 19, and 20, respectively,~~ and ~~[[a]] light chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65, respectively;~~

(f) ~~[[a]] heavy chain variable region that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 21, 22, and 23, respectively,~~ and ~~[[a]]~~

light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 78, 79, and 80, respectively;

(g) ~~[[a]]~~ heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 24, 25, and 26, respectively, and ~~[[a]]~~ light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65, respectively;

(h) ~~[[a]]~~ heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 27, 28, and 29, respectively, and ~~[[a]]~~ light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 84, 85, and 86, respectively;

(i) ~~[[a]]~~ heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 30, 31, and 32, respectively, and ~~[[a]]~~ light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequence consisting of SEQ ID NOs: 63, 64, and 65, respectively;

(j) ~~[[a]]~~ heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 33, 34, and 35, respectively, and ~~[[a]]~~ light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65, respectively;

(k) ~~[[a]]~~ heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 36, 37, and 38, respectively, and ~~[[a]]~~ light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 93, 94, and 95, respectively;

(l) ~~[[a]]~~ heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 39, 40, and 41, respectively, and ~~[[a]]~~ light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 96, 97, and 98, respectively;

(m) ~~[[a]]~~ heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising ~~[[the]]~~ amino acid sequences consisting of SEQ ID NOs: 42, 43, and 44, respectively,

and [[a]] light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 78, 79, and 80, respectively;

(n) [[a]] heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 45, 46, and 47, respectively, and [[a]] light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 102, 103, and 104, respectively;

(o) [[a]] heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 48, 49, and 50, respectively, and [[a]] light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65, respectively;

(p) [[a]] heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 51, 52, and 53, respectively, and [[a]] light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 108, 109, and 110, respectively,

(q) [[a]] heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 54, 55, and 56, respectively, and [[a]] light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 111, 112, and 113, respectively; and

(r) [[a]] heavy chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 57, 58, and 59, respectively, and [[a]] light chain variable region ~~that comprises~~ CDR1, CDR2, and CDR3 comprising [[the]] amino acid sequences consisting of SEQ ID NOs: 114, 115, and 116, respectively.

19. (Withdrawn) The antibody of claim 32 that comprises a heavy chain variable regions comprising the amino acid sequence of SEQ ID NO: 118.

20. (Withdrawn) The antibody of claim 32 that comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 120.

21. (Withdrawn) The antibody of claim 32 that comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118 and a light chain variable regions comprising the amino acid sequence of SEQ ID NO: 120.

22. (Withdrawn) The antibody of claim 32 that comprises the amino acid sequence of SEQ ID NO: 122 or 264.

23. (Currently Amended) The antibody of claim ~~[[16]]~~1, wherein ~~said~~ at least one of the heavy chain variable regions comprises a set of FR1, FR2, FR3, and FR4 sequences selected from the group consisting of ~~amino acid sequences of any one of:~~

- (a) SEQ ID NOs: 230, 232, 234, and 236;
- (b) SEQ ID NOs: 265, 267, 269, and 271;
- (c) SEQ ID NOs: 279, 281, 283, and 285;
- (d) SEQ ID NOs: 298, 299, 300, and 301; and
- (e) SEQ ID NOs: 298, 299, 306, and 301.

24. (Currently Amended) The antibody of claim ~~[[17]]~~1, wherein ~~said~~ at least one of the light chain variable regions comprises a set of FR1, FR2, FR3, and FR4 sequences selected from the group consisting of ~~amino acid sequences of any one of:~~

- (a) SEQ ID NOs: 239, 241, 243, and 245;
- (b) SEQ ID NOs: 272, 274, 276, and 278;
- (c) SEQ ID NOs: 302, 303, 304, and 305; and
- (d) SEQ ID NOs: 302, 307, 308, and 305.

25. (Currently Amended) The antibody of claim 1, comprising ~~18 that comprises a~~ heavy chain variable region ~~and a light chain variable region~~ of any one of:

(a) ~~[[a]] heavy chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 230, 232, 234, and 236, respectively,~~ and ~~[[a]] light chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 239, 241, 243, and 245, respectively;~~

(b) ~~[[a]] heavy chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 265, 267, 269, and 271, respectively,~~ and ~~[[a]] light chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 272, 274, 276, and 278, respectively;~~

(c) ~~[[a]] heavy chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 279, 281, 283, and 285, respectively,~~ and ~~[[a]] light chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 272, 274, 276, and 278, respectively;~~

(d) ~~[[a]] heavy chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 298, 299, 300, and 301, respectively,~~ and ~~[[a]] light chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 302, 303, 304, and 305, respectively; and~~

(e) ~~[[a]] heavy chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 298, 299, 306, and 301, respectively,~~ and ~~[[a]] light chain variable region which comprises FR1, FR2, FR3, and FR4~~  
~~having comprising~~ ~~[[the]] amino acid sequences consisting of SEQ ID NOs: 302, 307, 308, and 305, respectively.~~



26. (Currently Amended) The antibody of claim 1, wherein at least one of 32 that comprises a heavy chain variable region, wherein said heavy chain variable regions comprises the amino acid sequence of SEQ ID NO: 229, 256, 262, 289, or 295.

27. (Currently Amended) The antibody of claim 1, wherein at least one of 32 that comprises a light chain variable region, wherein said light chain variable regions comprises the amino acid sequence of SEQ ID NO: 238, 258, 291, or 297.

28. (Currently Amended) The antibody of claim 1, wherein ~~32 that comprises a heavy chain variable region and a light chain variable region of any one of:~~

(a) [[a]] at least one of the heavy chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 229, and [[a]]at least one of the light chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 238;

(b) [[a]] at least one of the heavy chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 256, and [[a]]at least one of the light chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 258;

(c) [[a]] at least one of the heavy chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 262, and [[a]]at least one of the light chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 258;

(d) [[a]] at least one of the heavy chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 289, and [[a]]at least one of the light chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 291; or

(e) [[a]] at least one of the heavy chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 295, and [[a]]at least one of the light chain variable regions comprises ~~comprising~~ the amino acid sequence of SEQ ID NO: 297.

29. (Withdrawn) The antibody of claim 32 that comprises the amino acid sequence of SEQ ID NO: 2, 254, 260, 287, or 293.

30.-31. (Canceled)

32. (Currently Amended) The antibody of claim 1, wherein the antibody recognizes an epitope within ~~An antibody that recognizes~~ the region of amino acids 26 to 274 of human Mpl (SEQ ID NO: 123).

33. (Currently Amended) The ~~[[An]]~~ antibody of claim 1, which has TPO agonistic activity.

34. (Withdrawn) A polynucleotide encoding an the antibody of claim 1.

35. (Withdrawn) A polynucleotide hybridizing to the polynucleotide of claim 34 under stringent conditions, wherein said polynucleotide encodes an antibody having binding activity against TPO receptor (Mpl).

36. (Withdrawn) A vector comprising the polynucleotide of claim 34.

37. (Withdrawn) A host cell that carries the polynucleotide of claim 34.

38. (Currently Amended) A pharmaceutical composition comprising ~~[[an]]~~ the antibody of claim 32.

39. (Withdrawn) The antibody of claim 32, wherein the antibody recognizes an epitope recognized by an antibody consisting of the amino acid sequence of SEQ ID NO:2.

40. (Withdrawn) The antibody of claim 32, wherein the antibody recognizes an epitope within the region of amino acids 189 to 245 of human Mpl.

41. (Withdrawn) The antibody of claim 32, wherein the antibody recognizes an epitope within the region of amino acids 213 to 231 of human Mpl.

42. – 43. (Canceled)

44. (New) A method of treating or preventing thrombocytopenia in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 38.

45. (New) A method for increasing platelet number in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 38.

46. (New) The method of claim 45, wherein the pharmaceutical composition is administered to the subject after the administration of platelet components to the subject.

47. (New) A method for increasing the amount of platelet components at the time of blood collection, the method comprising preadministering to a blood collection subject an effective amount of the pharmaceutical composition of claim 38.

48. (New) The method of claim 47, further comprising collecting blood from the subject after said preadministration.